UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: June 18, 2010

SUBJECT: **Tolfenpyrad.** Addendum to Human Health Risk Assessment for the Proposed Use of the New Active Ingredient on Ornamental Plants in Greenhouses.

PC Code: 090111	DP No.: D379231
Decision No.: 394868	Registration No.: 71711-GN
Petition No.: N/A	Regulatory Action: Section 3 Registration
Risk Assessment Type: Single Chemical, No aggregate	Case No.: N/A
TXR No.: N/A	CAS No.: 129558-76-5
MRID No.: N/A	40 CFR N/A

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This addendum to the Tolfenpyrad Human Health Risk Assessment dated June 3, 2010 (D354437) discusses the inhalation range-finding data submitted on June 14, 2010 by the Registrant, Nichino America, INC, as requested by HED. Additionally, HED is recommending changes to the proposed label to mitigate occupational risks associated with long-term postapplication dermal exposure.

Inhalation Toxicity Data

Background

A 4-week inhalation toxicity study (MRID 47447728) was submitted for tolfenpyrad. In the study, no adverse effects were noted up to 10 mg/m^3, the highest concentration tested (HCT). As stated in the study report, acute 6 hr and repeated dose inhalation range-finding studies were also conducted with tolfenpyrad. However, these studies were not made available to the Agency. As a result, HED requested these studies be submitted for review and this information has been received by the Agency.

The additional information indicated that in addition to the LC50 acute inhalation toxicity (MRID 47447734) study, two acute studies were conducted with tolfenpyrad, one 6 hr study at 26 mg/m^3 and another at 79 mg/m^3 (6 or 7 day recovery period). In the studies, mortality, body weight changes, and clinical signs (brown face staining, eye closure, and ataxia) were seen, with a dose related increase in the mortality observed (33% and 66%, respectively). Two repeated dose studies were also conducted with doses of 5 mg/m^3 or 10 mg/m^3. In the studies, effects were limited to slight decreases in body weight and ocular discharge at both doses. Based on the range-finding studies, 10 mg/m^3 was selected as the high dose for the 4-week inhalation study.

Conclusions

When considered together, the additional inhalation studies along with the previously submitted studies are adequate for risk assessment purposes. The no observed adverse effect level (NOAEL) for inhalation risk assessment is 10mg/m^3 based on the results of the 4 week inhalation toxicity study. The lowest adverse effect level (LOAEL) is 26 mg/m^3, based on effects seen in one of the acute range-finding studies. It is noteworthy to mention that the findings in the acute range-finding inhalation studies are inconsistent with those seen in the guideline acute (LC50) inhalation study previously submitted by the registrant. Mortality was observed in the range-finding study at much lower doses (37x) than seen in the LC50 study (excluding the HDT in the LC50 study). It is unclear to the Agency the reason behind the inconsistency although it is noted that the initial acute (LC50) study was conducted in a different laboratory facility.

Throughout the toxicological database (oral and inhalation studies), tolfenpyrad exposure (different durations) results in a steep dose response curve. Specifically, the doses where no effects are seen are generally only 2-3x lower than those resulting in mortality. In the case of the inhalation studies, there is a clear NOAEL identified in the 4-week inhalation study and this NOAEL was used for short- and intermediate-term inhalation exposure assessments. Although the Agency is not requiring additional inhalation toxicology data at this time, information on the potential effects of tolfenpyrad on mitochondrial inhibition and how it relates to human relevance would be helpful to better characterize the toxic effects seen in the tolfenpyrad database. Given the nature of the dose response curve and that mortality provides the critical effect for endpoint selection, and the absence of data on mode of action and human relevance, it

must be assumed that a small incremental increase in exposure could lead to significant adverse health outcomes for workers.

HED is in the process of updating policies/procedures related to both hazard and exposure aspects of inhalation risk assessment. As a result, the Agency may revisit the need for additional inhalation toxicity data in the future, as well as in the event of proposed new uses.

Label Recommendations for Long-term Postapplication Dermal Exposure

In HED's occupational exposure assessment (Z Figueroa; D366500; *Tolfenpyrad. Occupational Risk Assessment to Support Registration for the Proposed Use of the New Active Ingredient on Ornamental Plants in Greenhouses;* June 3, 2010), a margin of exposure (MOE) of 210 was calculated for long-term dermal postapplication high contact activities (i.e., cutting flowers). The level of concern (LOC) for this scenario is an MOE of 300, and therefore the MOE of 210 represents a potential risk concern for workers. In an effort to mitigate long-term dermal postapplication risk, the registrant has agreed to decrease the maximum single application rate from 1.36 lb ai/A to 0.95 lb ai/A. With the new application rate, the MOEs are greater than the level of concern (MOEs > 300) for workers harvesting ornamental plants grown for cuttings. Therefore, postapplication risks are no longer of concern.